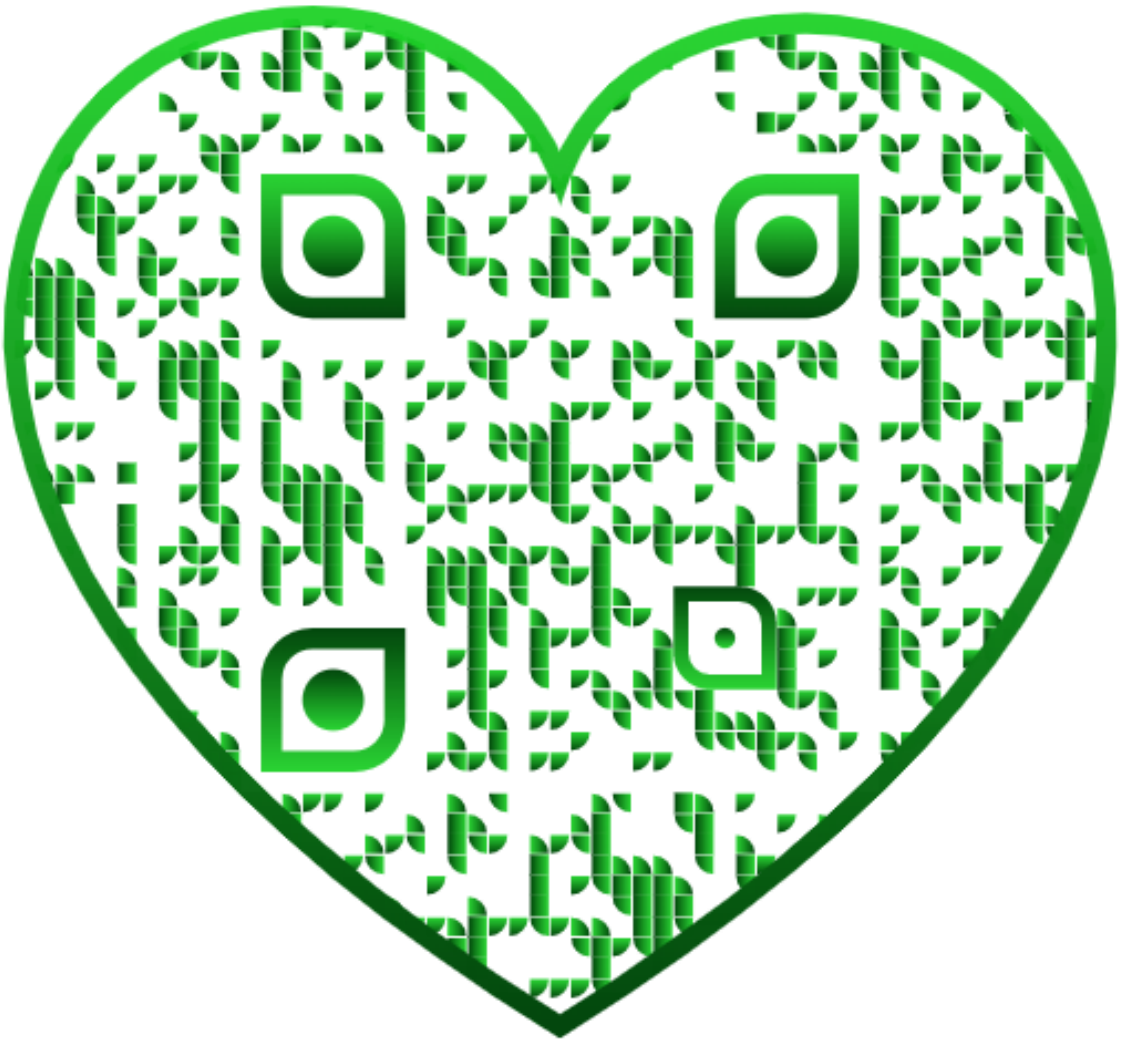
1. Introduction

- **Dosage Forms**
- **Routes of Drug Administration**
- **Pharmaceutical Ingredients**



Introduction, Dosage forms

- **Pharmaceutics**
  - A discipline of pharmacy that deals with all facets of the process of turning a new chemical entity (NCE) into a medication able to be safely and effectively used by patients in the community.
  - The science of dosage form design.
  - It encompass many subject areas, which are all associated with the steps to which a drug is subjected towards the end of its development

- **Drug**
  - Defined as an agent intended for use in the diagnosis, mitigation, treatment, cure, or prevention of disease in humans or in other animals.
- **Active Pharmaceutical Ingredient - API**
  - Is a chemical compound with pharmacological (or other direct effect) intended for used in diagnosis, treatment or prevention of diseases

- **Medicine (Drug product)**
  - A drug delivery system.
  - A means of administering drugs to the body in a safe, efficient, reproducible and convenient manner.

- **Pharmaceutical dosage form (Dosage form)**
  - Is a drug delivery system which is formed by technological processing (drug formulation)
  - This determines the physical form of the final pharmaceutical preparation
  - Must reflect therapeutic intentions, route of administrations, dosing etc.
  - Why we need a dosage form??

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- Direct clinical use of the API "as they are" is rare due to the number of good reasons:
  - API handling can be difficult or impossible (e.g., low mg and g doses)
  - Accurate drug dosing can be difficult or impossible
  - API administration can be impractical, unfeasible or not according to the therapeutically aims
  - Some API can benefit from reducing the exposure to the environmental factors (light, moisture…), or they need to be chemically stabilized due to the inherent chemical instability

- API can be degraded at the site of administration (e.g., low pH in stomach)
- API may cause local irritations or injury when they are present at high concentrations at the site of administration
- API can have unpleasant organoleptic qualities (taste, smell)
- Administration of active substance would mean to have no chance for modification (improvement) of its PK profile

- Therefore, drug substances are given as part of a formulation in combination with one or more non-medicinal agents that serve varied and specialized pharmaceutical functions.

- Selective use of these non-medicinal agents (pharmaceutical ingredients or excipients) produces dosage forms of various types.

- The pharmaceutical ingredients solubilize, suspend, thicken, dilute, emulsify, stabilize, preserve, color, flavor, and fashion medicinal agents into efficacious and appealing dosage forms.

- **Pharmaceutical preparation (PP)**
  - Particular pharmaceutical product containing active and inactive pharmaceutical ingredients formulated into the particular DF.
  - Packed and labeled appropriately.
  - Two major types of PP according the origin:
    - Manufactured in large scales by pharmaceutical industries (original and generic preparations)
    - Compounded individually in compounding pharmacies

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- PP manufactured by pharmaceutical industry:
  - These are the most frequent and favorable approach currently.
  - Such preparations must be approved by national authority.
  - There is a rigorous quality control (QC) and quality assurance (QA) during manufacturing.
  - Two types:
    - Original pharmaceutical preparations
    - Generic pharmaceutical preparations

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- PP compounded individually:
  - These PP are compounded individually for a particular patient.
  - It is highly advisable that whenever the particular suitable PP is approved and commercially available it should be preferred over the compounding.
  - The main advantage of compounded PP is the opportunity to individualize the pharmacotherapy.

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- Individually compounded PP can be a justified choice when:
  - The drug in a particular dosage form is not commercially available on the market,
  - The extraordinary low or high dose is needed (young children, elderly people, special situations – e.g., intoxications),
  - The patient suffers from the allergy on a specific excipient or another drug appearing in the PP.

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- The major disadvantage of PP compounded individually include:
  - The lack of standardization (it is always a "single-patient batch"),
  - Unavailability of rigorous QC testing and the appropriate clinical evaluation.

Dosage form Design

- Enhanced patient safety and therapeutic efficacy need the most suitable methods to deliver the drug.
- The methods may be designed to optimize bioavailability, minimize toxicity and side effects, and improve stability.
- A rational approach to dosage form design requires a complete understanding of the physicochemical and biopharmaceutical properties of the drug substance.

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- These properties of the drug are its:
  - pH solubility profile and dissolution rate,
  - Partition coefficient between lipoidal barriers and aqueous physiologic media,
  - Stability and/or degradation rate in the physiologic fluids,
  - Susceptibility to metabolic inactivation, and
  - Mechanism of transport through biologic membranes.

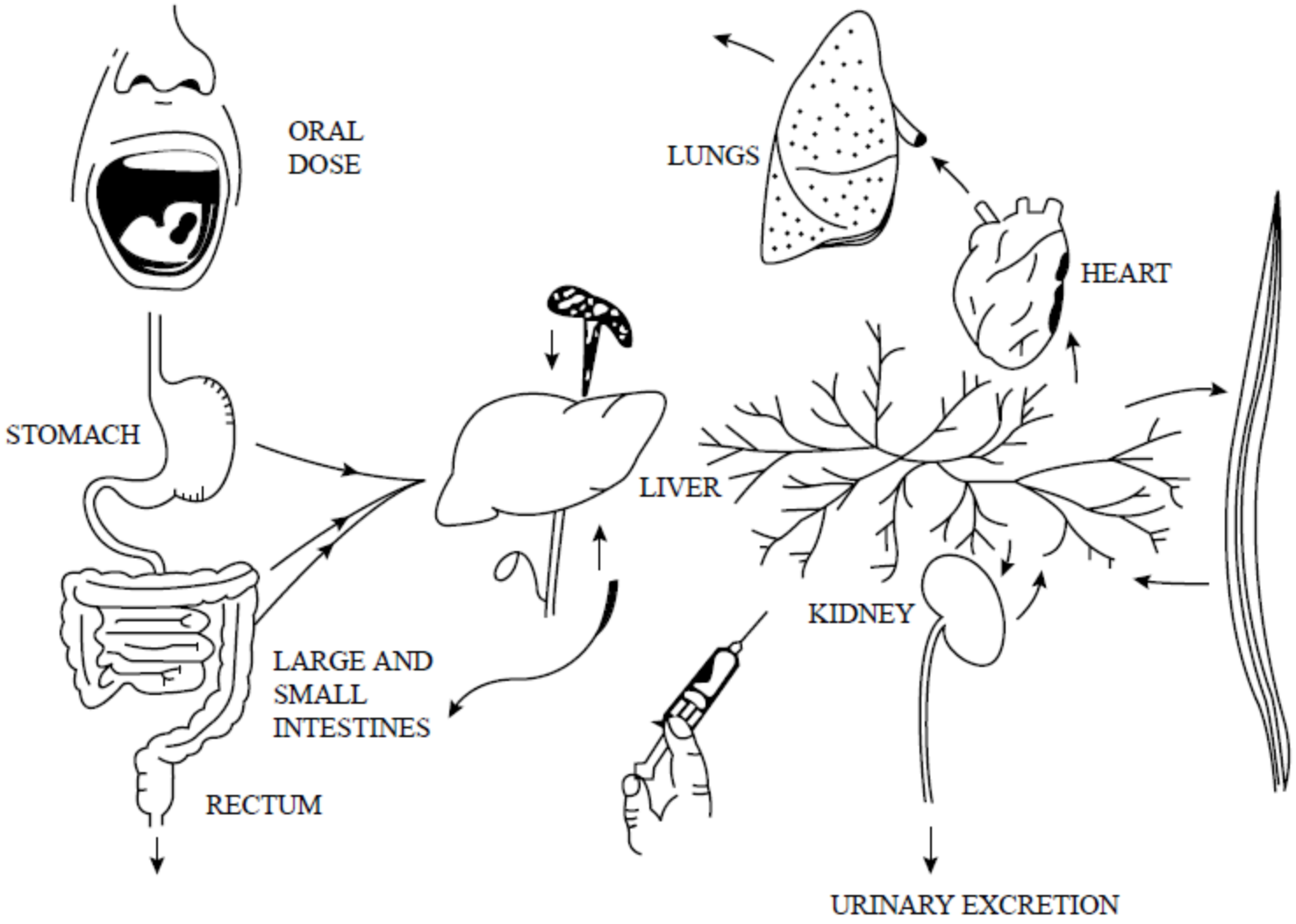

Fig. Physiological factors associated with bioavailability.

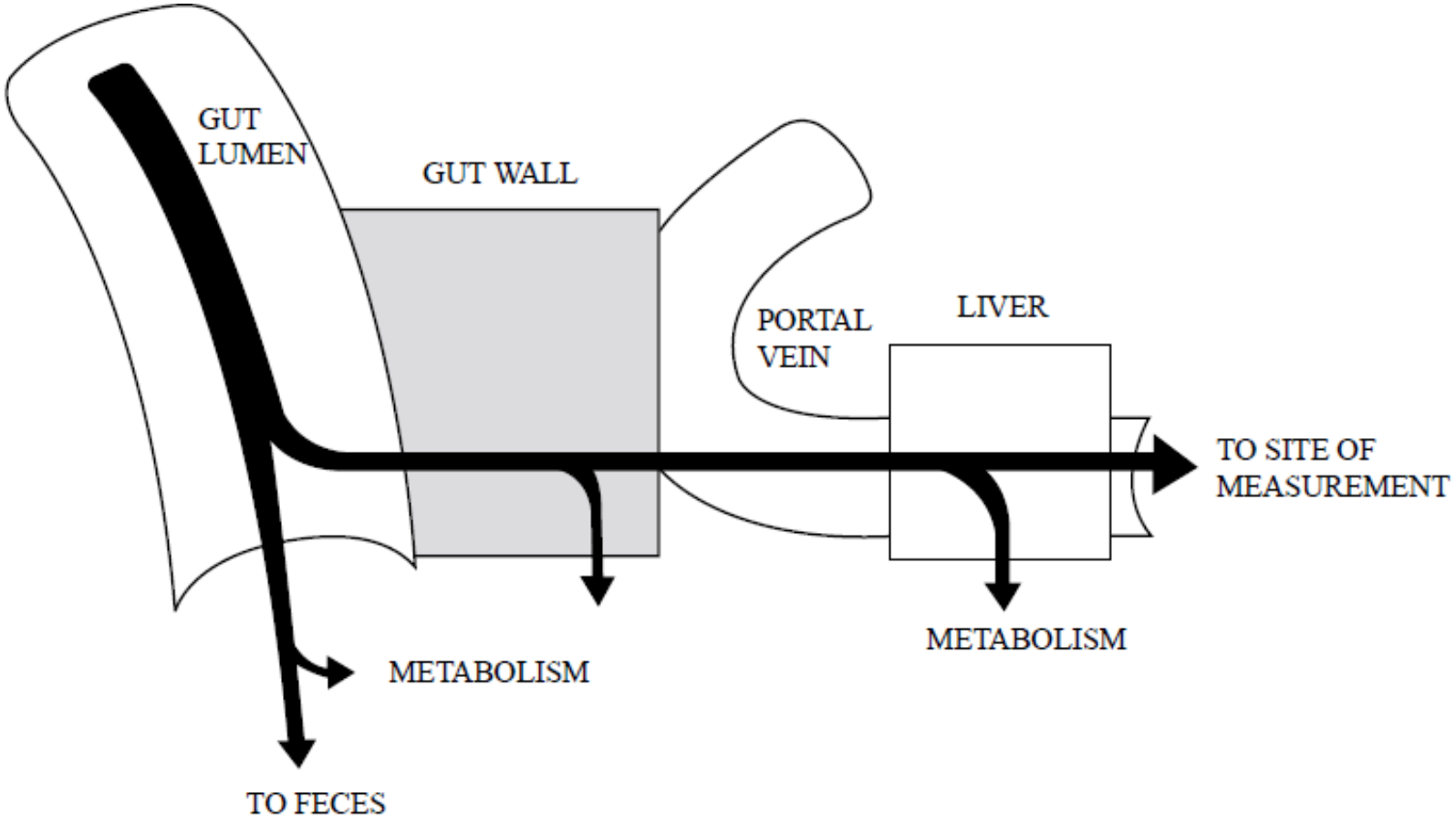

Fig. A drug, given as a solid, encounters several barriers and sites of loss

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- The aqueous solubility of a drug in the 2–8 pH range has a direct influence on its oral and parenteral formulations.
- Poor aqueous solubility is not always a limitation
- Sometimes it may be a desirable feature for a sustained effect after oral or parenteral administration.
- The lipid-aqueous partition coefficient of a drug molecule affects its absorption by passive diffusion.

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- Drugs intended for oral administration and can undergo rapid degradation at low pH may require protection from the acidic environment of the stomach.
- Metabolic inactivation of a compound following oral administration can occur in the GI lumen, the GI mucosa, or the liver.
- The site of metabolism and the susceptibility of the metabolic processes to saturation are factors that may influence oral bioavailability.
- Some of these factors may be altered to optimize oral bioavailability.

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Dosage form design: Formulation Approach

- Use of formulation techniques can improve the bioavailability and/or minimize the toxicity and side effects of drugs.

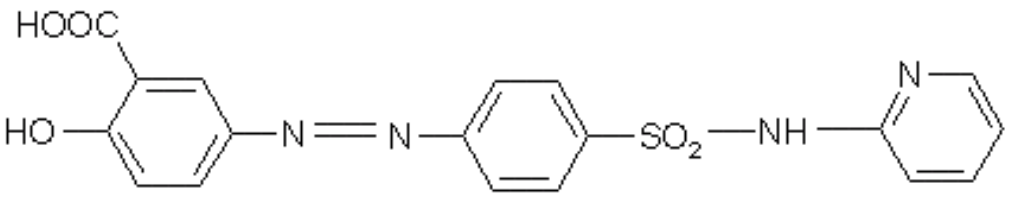
- Factors to consider include those that impact on solubility and dissolution rates, chemical and enzymatic stability, and absorption capability.

- Several parameters, including particle size, crystalline habit, and salt form, (can affect the solubility and dissolution rates of the drug); coating techniques and enzymatic protection (stability of a drug in the gut);

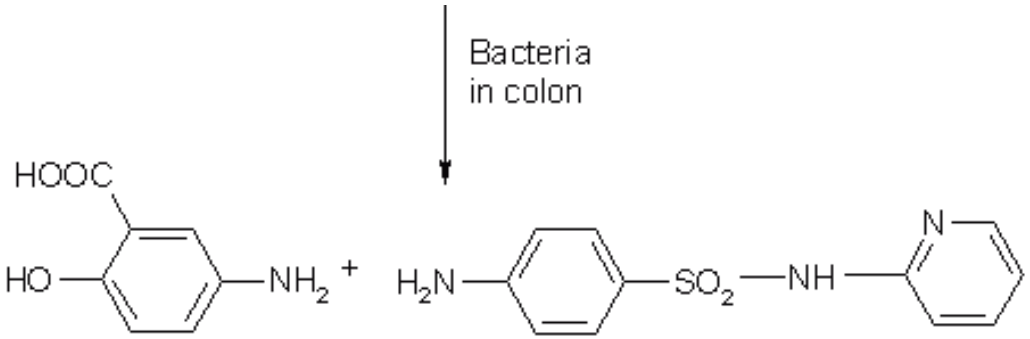
Dosage form design: Prodrug Approach

- A prodrug is defined as a drug that is prepared by chemically modifying a pharmacologically active species to form a new chemical entity that undergoes transformation to the active species within the body.

- Prodrugs can be used to increase or decrease the aqueous solubility, mask bitterness, increase lipophilicity, improve absorption, decrease local side effects, and alter membrane permeability of the parent molecule.



Sulphasalazine (prodrug)



5-aminosalicylic acid (active drug)

- The ideal prodrug should have the following characteristics:
  - Possess no pharmacologic activity,
  - Be eliminated more slowly than its rate of cleavage to the parent,
  - Be nontoxic,
  - Be inexpensive to prepare.

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Dosage form design: Device Approach

- Controlling the release of medication at the site of action is often desirable, especially for compounds that are absorbed rapidly through mucous membranes or are removed rapidly from the site of action.

- The approach normally reduces the systemic side effects of the agent.

- The system must be safe and biocompatible for biological application.

Dosage form design: Alternative Administration Routes

- The administration of drugs by alternative routes avoids absorption and metabolic barriers that may be present in the GI tract.
- The routes can also provide systematic availability when oral administration is contraindicated due to a physiologic condition, or the route may provide for a concentration-time profile that approaches intravenous dosing profiles.
- The ophthalmic, nasal, pulmonary, buccal, transdermal, and rectal routes provide one or more of these advantages.

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Classification of Dosage forms

- Dosage forms can also be **broadly** classified as:

1. **Homogenous systems** – one phase system

2. **Dispersion systems** – one phase (dispersed phase) is distributed throughout another one (continuous phase, dispersion medium)

    - According to the size of dispersed particles (1 nm – 0.5 mm) a molecular, **colloidal** and **coarse** dispersions can be distinguished

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- According to the overall **physical properties** of dosage forms (both homogenous and dispersion systems), we can classify dosage forms as:
  - Gaseous dosage forms
  - Liquid dosage forms
  - Semisolid dosage forms
  - Solid dosage forms

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- **Gases**
  - Gases – medicinal gases, inhalation/volatile anesthetics
  - Aero-dispersions of solid particles
- **Liquids**
  - Solutions
  - Emulsions
  - Suspensions

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- **Semisolid dosage forms**
  - A. Unshaped (without specific physical shape)
    - Gels, Creams, Ointments, Pastes
  - B. Shaped
    - Suppositories, Pessaries
- **Solid dosage forms**
  - A. Unshaped (without specific shape)
    - Powders for external/internal use
  - B. Shaped
    - Tablets, Capsules, Implantes, Transdermal patches…

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- Pharmaceutical dosage forms can also be classified according to the **intended use**:
  - For systemic administration
    - Oral (PO), Sublingual and buccal, Rectal, Parenteral, Transdermal, and Inhalational.
  - For local administration
    - Topical applications - On the skin or mucosa (the eye, nose, ear, the oral cavity, the vagina, rectum).

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- Pharmaceutical dosage forms can also be classified according to the **route of administration:**
  - **Inhaled** dosage forms
    - Aerosol, Gas, Inhaler & Metered dose inhaler, Solution for nebulizer
  - **Ophthalmic** dosage forms
    - Eye drop (solution or suspension), Ophthalmic gel, Ophthalmic ointment

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- **Oral** dosage forms
  - Capsule, Powder, Solution, Suspension, Tablet, Buccal or sublingual tablet, Thin film …
- **Otic** dosage forms
  - Ear drop (solution or suspension),
- **Parenteral** dosage forms
  - Solution or suspension for injection

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- **Rectal** dosage forms
  - Enema and Suppository
- **Topical** dosage forms
  - Cream, Ointment, Gel, Paste, Powder, Liniment, Lotion, Transdermal patch
- **Vaginal** dosage forms
  - Douche, Intrauterine device, Pessary, Vaginal ring, Vaginal tablet

Note

- The proper design and formulation of a dosage form requires consideration of the
  - Physical,
  - Chemical, and
  - Biologic characteristics

of all of the drug substances and pharmaceutical ingredients.

- The drug and pharmaceutical materials must be **compatible** with one another to produce a drug product that is stable, efficacious, attractive, easy to administer, and safe.

- The product should be manufactured with appropriate measures of quality control and packaged in containers that keep the product stable.

- The product should be labeled to promote correct use and be stored under conditions that contribute to maximum shelf life.

Introduction, Routes of drug administration

- The effective dose of a drug may vary with the dosage form and the route of administration.
  - Drugs administered intravenously enter the blood stream **directly** and **completely**.
  - In contrast, drugs administered orally are rarely fully absorbed into the blood stream because of the various physical, chemical, and biologic barriers to their absorption.

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- Varying rates and degrees of absorption can occur from drug administration in different routes.
- One of the fundamental considerations in dosage form design is whether the drug is intended for local or systemic effects.
  - Local effects are achieved by direct application of the drug to the desired site of action, such as the eye, nose, or skin.
  - Systemic effects result from the entrance of the drug into the circulatory system and transport to the cellular site of its action.

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- An individual drug substance may be formulated into multiple dosage forms that result in different drug absorption rates and times of onset, peak, and duration of action.

- The difference in absorption between dosage forms is a function of the formulation and the route of administration.

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- Routes of drug administration can broadly be divided into three categories:
  - **Topical**: local effect, substance is applied directly where its action is desired.
  - **Enteral**: desired effect is systemic (non-local), substance is given via the digestive tract.
  - **Parenteral**: desired effect is systemic, substance is given by routes other than the digestive tract.

TERM	SITE
Oral	Mouth
Peroral (per os[a])	Gastrointestinal tract via mouth
Sublingual	Under the tongue
Parenteral	Other than the gastrointestinal tract (by injection)
Intravenous	Vein
Intra-arterial	Artery
Intracardiac	Heart
Intraspinal or intrathecal	Spine
Intraosseous	Bone
Intra-articular	Joint
Intrasynovial	Joint fluid area
Intracutaneous, intradermal	Skin
Subcutaneous	Beneath the skin
Intramuscular	Muscle
Epicutaneous (topical)	Skin surface
Transdermal	Skin surface
Conjunctival	Conjunctiva
Intraocular	Eye
Intranasal	Nose
Aural	Ear
Intrarespiratory	Lung
Rectal	Rectum
Vaginal	Vagina

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Oral Route

- This is the most frequently used route of drug administration.
  - It is considered to be the most natural, uncomplicated, convenient, and safe means of administering drugs.
  - However, the oral route is associated with slow drug response; chance of irregular absorption of drugs; and destruction of certain drugs.

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- Most drugs are taken orally for the systemic effects that result after absorption, but a few drugs, such as antacids, are swallowed for their local action in the GIT.
- One of the problems associated with the oral administration of a drug is first-pass effect (Read more).
- Various pharmaceutical dosage forms can be administered orally (tablets, capsules, suspensions, and solutions)

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Rectal Route

- The rectal route can be used effectively to treat local conditions and to deliver drugs systemically.
  - Local effect is desired in the case of pain and itching, mostly due to the occurrence of hemorrhoids.
  - For a systemic effect all orally given drugs can be used.

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- Rectal administration for systemic action may be preferred:
  - For drugs destroyed or inactivated by the environments of the stomach and intestines.
  - When the oral route is precluded because of vomiting or when the patient is unconscious or incapable of swallowing drugs safely without choking.
- Solutions, suppositories, or ointments can be administered rectally.

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Parenteral Route

- A drug administered parenterally is one injected into the body at various sites and to various depths.
  - Intravenous, Intra-arterial, Intracardiac, Intraspinal/intrathecal, Intraosseous, Intra-articular, Intrasynovial, Intracutaneous, intradermal, Subcutaneous, Intramuscular…
  - Subcutaneous, intramuscular, and intravenous administrations are the three primary routes of parenteral administration

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- The parenteral route is preferred:
  - For drugs destroyed or inactivated in the gastrointestinal tract or too poorly absorbed,
  - When rapid absorption is essential,
  - For patients who are uncooperative, unconscious, or otherwise unable to accept oral medication.
- Once the drug is injected parenterally, there is no retreat.

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- Most injectable preparations are either a sterile suspension or solution of a drug substance in water or in a suitable vegetable oil.

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Subcutaneous Injections

- The subcutaneous (hypodermic) administration of drugs entails injection through the skin into the loose subcutaneous tissue.
  - Generally given in the forearm, upper arm, thigh, or buttocks.
  - It is best to alternate injection sites to reduce tissue irritation.
  - Insulin is an example of a drug administered by the subcutaneous route.

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Intramuscular Injections

- Intramuscular injections are performed deep into the skeletal muscles, generally the gluteal or lumbar muscles.
  - The selected site is where the danger of hitting a nerve or blood vessel is minimal.
- Aqueous or oleaginous solutions or suspensions may be used intramuscularly.

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- Drugs that are irritating to subcutaneous tissue are often administered intramuscularly.
- Larger volumes may be administered intramuscularly than subcutaneously.

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Intravenous Injections

- Injection directly into the vein at a rate commensurate with efficiency, safety, comfort to the patient, and the desired duration of drug response.

- Drugs may be administered IV as a single, small-volume injection or as a large-volume slow IV drip infusion.

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- It is essential that the drug be maintained in solution after injection and not be precipitated within the circulatory system, an event that might produce emboli.

- Because of a fear of the development of pulmonary embolism, oleaginous vehicles are not usually intravenously administered.

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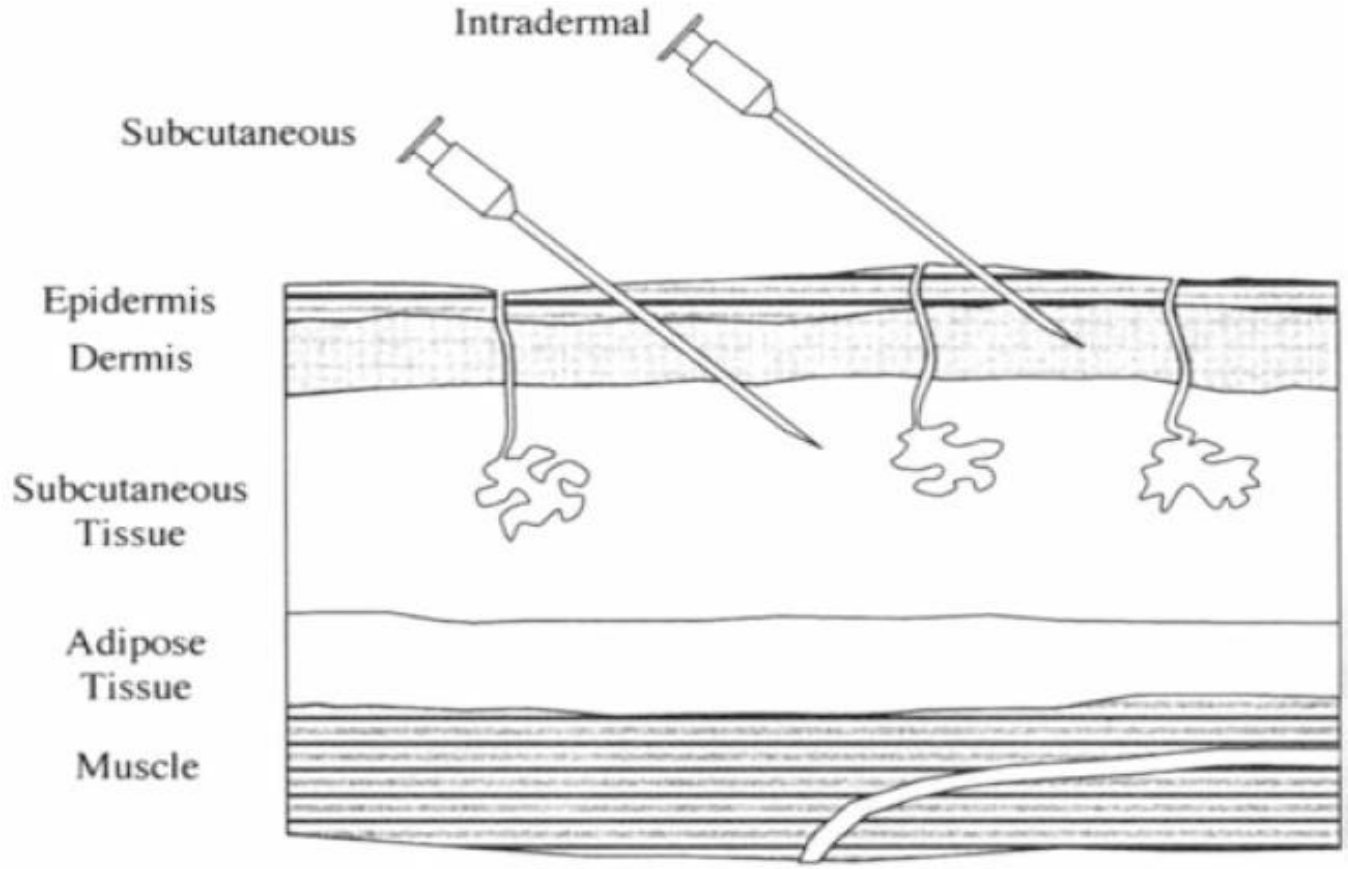
Intradermal Injections

- Intradermal injections are administered into the corium of the skin, usually in volumes of about 0.1 mL.

- The injections are frequently performed as diagnostic measures, as in tuberculin and allergy testing.


Intradermal
Subcutaneous
Epidermis
Dermis
Subcutaneous Tissue
Adipose Tissue
Muscle

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Topical Route/Transdermal Administration

- Drugs are administered topically, or applied to the skin, for their action at the site of application (topical) or for systemic drug effects (transdermal).

- Different types of preparations can be applied topically: ointments, creams, pastes, lotions, powders, and patches.

- Drugs are also applied topically to the eye, ear, and mucous membranes of the nose.

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- Drugs that are absorbed (transdermally) enter the skin by way of the pores, sweat glands, hair follicles, sebaceous glands, and other anatomic structures of the skin's surface.
  - This route can avoid first-pass metabolism.
  - It provide a large surface area for continuous-controlled administration of drugs with short biological half-lives and narrow therapeutic indices.
  - Absorption can be enhanced with molecules that maintain an appropriate hydrophilic–lipophilic balance.

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- Limitations:
  - Inability of the skin to deliver large doses,
  - The relatively slow plasma increase when compared with other routes, and
  - The potential for irritation.

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Ophthalmic Route

- Used traditionally for topical application for local effects, it can also be considered for systemic drug delivery also.
- Drugs (especially peptides) can be absorbed from the mucosa during tear turnover as well as via the blood vessels of the conjunctiva.
- Drawbacks: sensitivity of the eye to irritation and formulation is frequently washed away.

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Nasal Route

- This route produces rapid blood levels and rapid responses that approach those obtained from intravenous dosing.
- In addition, first-pass metabolism is avoided.
- Recently the nasal route has received as a convenient and reliable route for the systemic administration of drugs, especially those that are ineffective orally

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- It would appear that the nasal route could be considered for drugs that meet the following criteria:
  - Ineffective orally,
  - Used chronically,
  - Used in small doses; and
  - Desirable to have rapid entry to the general circulation.

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- Drawbacks:
  - Hydrolysis in the nasal cavity,
  - Small volume permitted (i.e., 0.2 ml or less),
  - The potential for irritation, and
  - Effect of formulation components upon long-term use

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Buccal and Sublingual Routes

- Absorption from the buccal and sublingual vasculature and lymphatics bypasses hepatic circulation and, thereby, reduces first-pass metabolism.

- The driving force of absorption is the high thermodynamic activity of the compounds.

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- Drawbacks:
  - The requirement for successful candidates to possess high thermodynamic activities,
  - The restrictive size of the buccal pouch and sublingual area, and
  - The concern over the palatability and local irritation by the compound.

2. Pharmaceutical Ingredients

Introduction, Pharmaceutical ingredients

- Pharmaceutical ingredients (excipients) are required to produce a drug substance in a final dosage form.
- Almost all dosage forms include excipients.
- The total amount of excipients frequently used is greater than the amount of the API in a dosage form.
- Excipients are expected to be inactive ingredients.

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- Variability in the performance of an excipient is a key determinant of dosage form performance.

- Excipients are expected to have some defined functional roles in pharmaceutical dosage forms.

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- Some of the functional roles of excipients include:

1) Modulating solubility and bioavailability of the API;

2) Enhancing stability of the API in finished dosage forms;

3) Helping API maintain a preferred polymorphic form or conformation;

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4) Maintaining pH and osmolarity of liquid formulations;

5) Acting as antioxidants, emulsifying agents, aerosol propellants, tablet binders, and tablet disintegrants, etc;

6) Preventing aggregation or dissociation; and

7) Modulating the immunogenic response of API (e.g., adjuvants) and many others.

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- There is some psychologic basis to drug therapy.
  - The odor, taste, and color of a pharmaceutical preparation can play a part.
- Most drug substances are unpalatable and unattractive in their natural state.
  - However, excipients present them to the patient as colorful, flavorful formulations attractive to the sight, smell, and taste.

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- An appropriate drug has its most beneficial effect when it is accepted and taken properly by the patient.
  - The proper combination of flavor, fragrance, and color in a pharmaceutical product contributes to its acceptance.
- An "electronic tongue" is used to aid in providing a "taste fingerprint" during formulation development.
  - This device provides information on taste levels and the stability of flavors in terms of taste.

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Flavoring agents

- Primarily intended to liquids intended for oral administration.
- Medication in liquid form comes into immediate and direct contact with these taste buds.
  - The taste receptor cells interact with molecules dissolved in the saliva and produce a taste sensation.

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- There are four general distinctions of flavor: sweet, acid/sour, salty, and bitter.
- The selection of an appropriate flavoring agent depends on several factors, including:
  - The taste of the drug substance itself.
  - Individuals' tastes and flavor preferences.
  - The age of the intended patient.

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- Certain flavoring materials are more effective than others in masking or disguising the particular taste of a drug:
  - Cocoa-flavored vehicles – for masking the taste of **bitter** drugs
  - Fruit or citrus flavors – for **sour or acid-tasting** drugs
  - Cinnamon, orange, raspberry – for **salty** drugs more palatable.

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- Geriatric and pediatric patients are often very different in their preferences for taste.
  - Children prefer sweet candy-like preparations with fruity flavors
  - Adults seem to prefer less sweet preparations with a tart rather than a fruit flavor.

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- Flavors must be carefully selected and checked for stability.
  - They can degrade as a result of exposure to light, temperature, oxygen, water, enzymes, contaminants, and other product components.
- Three basic types of flavors:
    - Natural flavors
    - Artificial flavors
    - Spices

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Sweetening agents

- A sweetening agent can play a number of important roles in an oral liquid formulation such as enhancing flavor, masking bitter taste, and/or increasing viscosity.

- Two classes of sweeteners:

  - Natural Sweeteners (e.g. Sucrose)

  - Artificial Sweeteners

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- Typically, the concentration of sweeteners in oral liquids averages between 30% and 50% of the formulation.
- In some cough or cold syrups, the sweetener content is as high as 80%.
  - Concerns – (when using higher concentrations of sweeteners):
    - Diabetic patients,
    - Risk of microbial contamination and growth,
    - Risk of crystallization

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- Artificial sweeteners are generally very sweet as compared to sucrose.
  - This results in a much lower concentration needed in the formulation.
  - Also help to formulate a "sugar-free" formulation for diabetic patients.

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Coloring agents

- These are used for **esthetic** purposes.
- Most pharmaceutical colorants in use today are synthetic.
- Generally, colors are used to match the flavor or color changes of an oral liquid formulation.

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- Pharmaceutical coloring agents are divided into two groups:
  - Coloring agents that are soluble in water (**dyes**)
  - Coloring agents that are insoluble in water (**pigments**)

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- The amount of colorant generally added to liquid preparations ranges from 0.0005% to 0.001% depending upon the colorant and the depth of color desired.

- Because of their color potency, dyes generally are added in the form of diluted solutions rather than as concentrated dry powders.

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- Many coloring agents are poorly compatible or incompatible with citric acid, ascorbic acid, gelatin, glucose, lactose, sodium bicarbonate, and saccharose solutions.

- Additionally, several groups of dyes have been associated with serious adverse effects.

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- In addition to esthetics and the certification status of a dye, its physical and chemical properties has also to be considered.
  - A prime importance is the solubility of a dye in the vehicle to be used for a formulation.
  - pH and pH stability of the preparation to be colored.
    - Dyes can change color with a change in pH.
  - Photostability

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Preservatives

- Pharmaceutical preparations needs preservation against:
  - Chemical and physical degradation due to changed environmental conditions.
  - Microbial contamination.

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- Preparations that provide excellent growth media for microbes are most aqueous preparations.
- Some desirable features of anti-microbial preservatives:
  - A wide spectrum of activity against all bacteria, yeasts and molds;
  - Bactericidal rather than bacteriostatic activity;

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- Freedom from toxic, irritant or sensitizing activity;
- High water solubility.
- Compatibility with the other ingredients and with the container.
- Stability and effectiveness over a wide range of pH and temperatures;
- Freedom from color and odor;
- Retention of activity in the presence of large numbers of microorganisms.

PRESERVATIVE	PROBABLE MODES OF ACTION
Benzoic acid, boric acid, p-hydroxybenzoates	Denaturation of proteins
Phenols and chlorinated phenolic compounds	Lytic and denaturation action on cytoplasmic membranes and for chlorinated preservatives, also by oxidation of enzymes
Alcohols	Lytic and denaturation action on membranes
Quaternary compounds	Lytic action on membranes
Mercurials	Denaturation of enzymes by combining with thiol (-SH) groups)

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Buffers and pH Adjusting Agents

- Without the ability to control the formulation pH, there may be large changes during storage, based on water loss, or carbon dioxide and oxygen access.
- Most formulations utilize a buffer to control potential changes in pH.

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- The selection of a suitable buffer should be based on:
  - Whether the acid–base forms are listed for use in liquids formulations,
  - The stability of the drug and excipients in the buffer, and
  - The compatibility between the buffer and container.

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- The stabilizing effect of buffers should also be investigated to determine the potential reaction between excipients and API.
  - Buffers that use carbonates, citrate, tartrate, and various phosphate salts may precipitate with calcium ions by forming sparingly soluble salts.
- There are a number of factors that may also affect the solution pH such as temperature, ionic strength, dilution, and the amount and type of cosolvents present.

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Antioxidants, Chelating Agents, And Sequestrants

- The oxidation of an API can be difficult to control due to:
  - The presence of trace amounts of impurities, which may be present from the API or excipient vendor, and
  - Oxidation (and photolysis) have relatively low activation energies.

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- Antioxidants can be:
  - Compounds that can reduce a drug that has been oxidized, or
  - Compounds that are more readily oxidized than the agents they are to protect (oxygen scavengers).
- Antioxidants can also act as chain terminators, reacting with free radicals in solution to stop the free-radical propagation cycle.

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Other Pharmaceutical Excipients

- Pharmaceutical Solvents
- Viscosity-inducing Agents
- Surfactants and Emulsifying Agents
- Ointment Bases
- Suppository Bases
- Gelling agents
- Diluents, disintegrants, lubricants, binder and adhesives